Cite No. 1

FENOFIBRATE TABLETS 54-160 MG

DISSOLUTION TEST CONDITIONS DEVELOPMENT STUDIES,

DISSOLUTION TEST SPECIFICATION RECOMMENDATIONS

1. INTRODUCTION :

The Fenofibrate tablets correspond to a new formulation which was developed to improve the dissolution performances of the marketed Fenofibrate capsules. This new formulation combines the well established particle size reduction effect with a new coating process and consists of the drug particle dispersion into a highly hydrophilic PVP (polyvinylpyrrolidone) network. This new process results in an enhancement of both disintegration and dissolution steps.

This report is focused on dissolution condition development.

2. MATERIALS

2.1. FENOFIBRATE TABLETS:

Quantitative composition :

Item	component	Amount (mg/tablet)	
		54 mg	160 mg
1	Fenofibrate	54.0	160.0
2	Lactose, monohydrate	46.7	138.4
3	Sodium Lauryl Sulfate	1.9	5.6
4	Crospovidone	32.4	96.0
5	Povidone	54.0	160.0
6	Sodium Stearyl Fumarate	2.2	6.4
7	Microcristalline cellulose	38.8	115.0
8	Colloidal Silicon Dioxide	4.3	12.6
9	Opadry ® OY-B-32830 (yellow)	11.0	
	Opadry ® OY-B-28290 (white)		28.0
10	Purified Water *	--	--

*Purified Water was removed during the drying process

The process consisted of a coating by spraying a micronized fenofibrate - PVP aqueous suspension onto an inert lactose support following by a milling of resulting dry granulate and a blending with the external phase components. Tablets were film coated with an Opadry®.

2.2. FENOFIBRATE CAPSULES (TRICOR® 67 MG)

Quantitative composition:

Item	Component	Amount (mg/capsule)
1	Fenofibrate	67.0
2	Lactose, monohydrate	33.8
3	Sodium Lauryl Sulfate	2.4
4	Pregelatinized Starch	10.1
5	Crospovidone	2.3
5	Magnesium Stearate	1.7
6	Purified Water *	–

*Purified Water was removed during the drying process

The capsules were manufactured according to the following process i.e. a wet granulation of the internal phase prior to the final blending with external phase components and the capsule filling.

2.3. BATCH NOMENCLATURE :

- 160 mg Fenofibrate uncoated tablets : RG 2401/01 - 2403/01; batch Size : around 20,000 tablets (i.e. 13.5 Kg bulk), Lab scale production
- 160 mg Fenofibrate coated tablets : Bulk Lot : Fournier Batch Number 7, Abbott Lot 47-813-AL, Batch size : 432,276 tablets, 100% of production full scale
- 54 mg Fenofibrate coated tablets : Bulk Lot : Fournier Batch Number 2, Abbott Lot 47-800-AL, Batch size : 320,512 tablets, 100% of production full scale
- 67 mg Fenofibrate capsules (TRICOR® 67 mg) : Bulk Lot : Fournier Batch Number 032, Abbott Lot 41-032-3T-21, Batch size : 2,901,957 capsules, 100% of production full scale

3. METHODS :

3.1. DISSOLUTION TEST GENERAL PROCEDURE :

Dissolution test were carried out on six (hardness effect study) or twelve units using USP Dissolution Apparatus 2 (paddle speed at 75 rpm), in 1000 mL of 0.025 or 0.05M Sodium Lauryl sulfate (SLS) at 37 °C excepted during the preliminary study which was conducted at various paddle speeds and Sodium Lauryl Sulfate aqueous media. The amount of released drug was essayed using an ultraviolet Spectrophotometer at the wavelength of maximum absorbance (approximately 291 nm).

3.2. BIOAVAILABILITY STUDIES :

These were phase I, single - dose, non fasting, open label, randomized, two - period, crossover, single center studies (protocol M98-961 & M98-962) in a total of 42 healthy adult male and female volunteers.

The formulations were administered orally with 180 mL of water, 5 minutes after completion of a standard breakfast (30% fat).

Blood samples were collected at the following times 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 48, 72 ,96, and 120 hours after each administration. Plasma samples were analyzed using an HPLC - UV method in order to measure the corresponding plasma concentrations of fenofibric acid.

Protocol M98-961 consisted of a comparison the bioavailability of Fenofibric Acid from a 54 mg tablet of micronized Fenofibrate (Bulk Lot 47-800-AL ; L.F. Lot 2) with that from a 67 mg capsule (size 4) of micronized Fenofibrate (TRICOR® - Bulk Lot 41-032-3T-21 ; L.F Lot 032).

Protocol M98-962 consisted of a comparison the bioavailability of Fenofibric Acid from a 160 mg tablet of micronized Fenofibrate (Bulk Lot 47-813-AL ; L.F. Lot 7) with that from a 67 mg capsule (size 4) of micronized Fenofibrate (TRICOR® - Bulk Lot 41-032-3T-21 ; L.F. Lot 032).

4. SELECTION DISSOLUTION TEST CONDITIONS :

The fenofibrate is a neutral, lipophilic compound (log P = 5.24) which is practically insoluble in water (aqueous solubility < 0.5 mg/L). In such a case, the dissolution test can not be conducted in common aqueous medium and addition of surfactant can represent an objective alternative. Based on the Fenofibrate solubility data obtained in various Sodium Lauryl Sulfate aqueous media (table 1), this surfactant is relevant to prepare the dissolution medium. To ascertain the amount of SLS, various dissolution media were tested and evaluated according to the following criteria :

- ability to dissolved 75 - 80 % of the drug within period of time 30- 60 minutes based on compendial dissolution requirements
- ability to discriminate different formulations and voluntary process changes
- ability to fit the in vivo data

Table I : Fenofibrate solubilities in various SLS aqueous solutions

SLS concentration	Fenofibrate saturated concentration
SLS 0.025M (7.21 g/L)	About 220 mg
SLS 0.05M (14.42 g/L)	About 600 mg
SLS 0.1M (28.84 g/L)	About 1200 mg

4.1. PRELIMINARY STUDY :

This study was performed on 160 mg strength uncoated tablets (lab scale batch RG 2401/01). The dissolution tests were conducted at variable conditions in order to evaluate the paddle speed and SLS concentration effects. For each variable the corresponding levels tested were:

- paddle speeds : 50 - 75 - 90 -120 rpm (except at 0.1 M SLS medium where the 120 rpm was suspended regarding the initial results).
- SLS concentrations : 0.025 M - 0.05 M - 0.1 M

The dissolution tests were performed on six units per batch and according to the general procedure described section 3.1. In this case, the dissolution profiles were defined from samples collected at least at the following time 0 10 15 20 minutes additional sampling were adapted when required.

The results are reported in appendix 1.

There is no speed-effect over 75 rpm for the three dissolution media. The 50 rpm paddle speed dissolution profiles shows a lowering of 10 units or less during the first 30 minutes depending of the medium. The percentage of dissolution increases with increasing SLS concentrations.

Based on these results :

- The 75 rpm paddle speed is selected, since it represents the minimal value at which the dissolution results are independent of a speed effect. Furthermore this paddle speed is consistent with testing conditions applied for TRICOR® capsules.
- Although it does not allow to have sink conditions, where 0.05M SLS is necessary, the 0.025 M SLS medium is preferred to characterize the dissolution kinetics since it should have more discriminating property, the drug release period is in accordance with the general compendial time requirements (30-60 minutes) and is in agreement with the approach described by V. P Shah. (International Journal of Pharmaceutics 125 :99-106).

So the provisional selected dissolution conditions are :

- medium 1 liter of 0.025 M SLS aqueous medium
- paddle speed : 75 rpm

4.2. DISCRIMINATORY ABILITY EVALUATION :

This study was conducted to evaluate the ability of the selected conditions to discriminate objective variations and, firstly, consists of dissolution profile comparisons of lab scale batches exhibiting various hardness values (tablets strength 160 mg).

The dissolution profiles were compared using a model independent method based on Similarity (f2) and Difference (f1) Factors.

The dissolution tests were conducted on six tablets according to the general method previously described in section 3.1. Data and dissolution profiles are reported in appendix 2

Based on these results, the selected dissolution conditions seems to be adequate to discriminate unexpected production hardness variation, since a 59N difference results in calculated f1(10.4) and f2 (53.3) values highly closed to reject limits (<15 and >50 respectively) and ensures a sameness of curves when the hardness variation is in common limit of 42N with respective f1 and f2 values at 4.8 and 70.0.

This discriminatory power evaluation of the set dissolution conditions was completed by a comparative analysis of the dissolution and absorption data issued from the 3 industrial batches used in the two pivotal bioequivalence studies (M98-961 & M98-962).

The dissolution tests were conducted on twelve units per lot according to the selected conditions for tablets (0.025M SLS - 75 rpm) and TRICOR® specified procedure (0.05M SLS - 75 rpm).

The corresponding results are reported in tables VI and VII.

In both cases, 54 mg and 160 mg Fenofibrate tablets shows a faster Fenofibrate release than the 67 mg TRICOR® capsules as expected. However, some variability regarding the quantitative response is noted.

For the 0.05M medium, the tablet dissolution profiles are independent of the strength except at the 10 minutes time point and result in quantitative differences from 30 to 10 units between the capsule and tablets.

For the 0.025M medium, the strength effect on tablet dissolution profiles is discernible until 20 minutes and a more significant difference of at least 20 units is obtained between capsules and both tablets.

A comparative approach based on the f1 and f2 factors is excluded regarding the recommendations generally set (« only one measurement should be considered after 85 % dissolution » ie restricted to 2 points per comparison)

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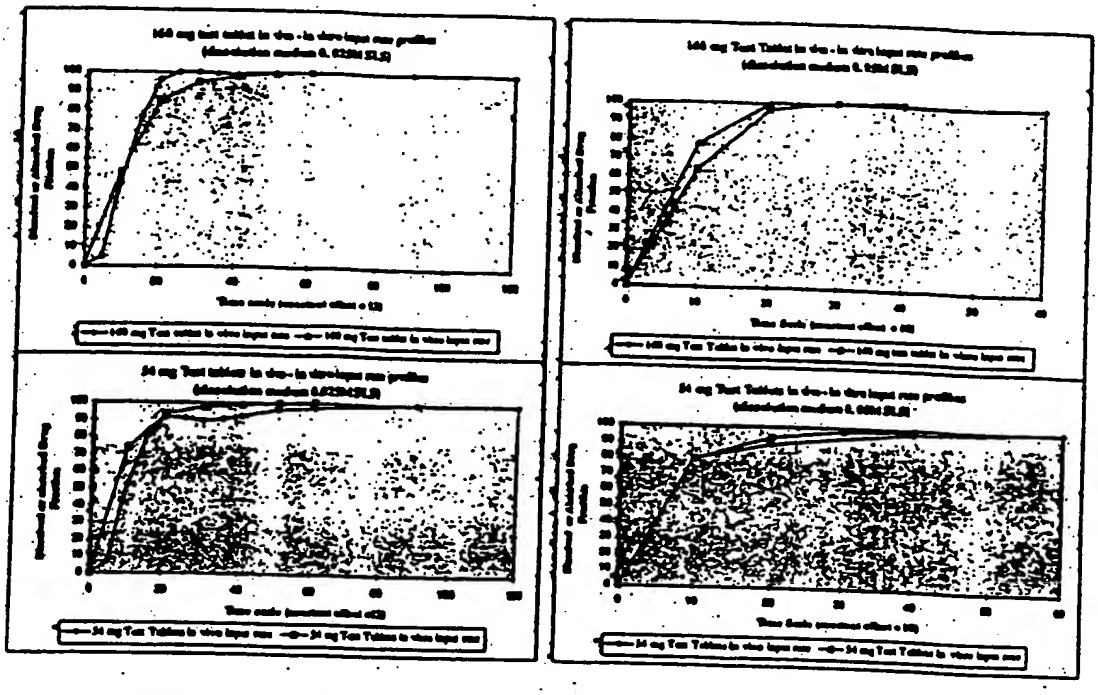
4.3. IN VITRO - IN VIVO COMPARISON

The two dissolution testing methods were then evaluated towards their ability to mimic the in vivo release profiles by comparing the in vitro dissolution and in vivo input curves. This was done by deconvolution of the tablets plasma level data using the mathematical Loo Riegelman procedure (appendix 3). The relation between the in vitro and in vivo deconvoluted data was assess by a point to point comparison using constant offset values of 12 or 18. These time offsets were necessary to fit the two curves with a consistent scale of time. The results for each medium and dosage are presented hereafter.



The two media presented an equivalent ability to describe the in vivo data however the 0.025M medium allowed a more accurate fitting of the ascending section of the curves due to a more adequate constant offset value.

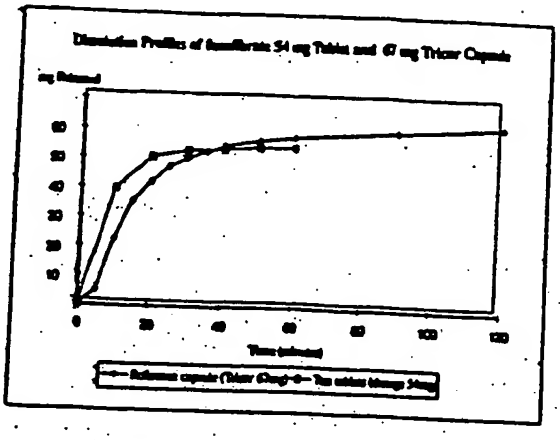
In accordance with our aforementioned criteria, the provisional dissolution method was then confirmed ie :

- Apparatus 2 , 1liter of 0.025M aqueous medium, paddle speed 75 rpm.

5. DISSOLUTION SPECIFICATION RECOMMENDATION :

For 54 mg and 160 mg strength tablets, a single - point specification can be set as a routine quality control test considering their fast release profile in the selected medium.

To ensure a independent strength response, a time test up to 20 minutes should be selected. The two bioequivalent drug products, 54 mg fenofibrate tablets and TRICOR® 67 mg fenofibrate release the same amount of fenofibrate at the dissolution profiles meeting point which is at 40 minutes. This time is selected to specify the tablet dissolution.



At 40 minutes, average dissolution of the biobatches is complete : 98 - 99% of the label. To take into account the individual fenofibrate content variation, ± 15% label content, which may conduct to 85% fenofibrate dissolved in one tablet, a dissolution specification of Q = 80% in 40 minutes is recommended in accordance with the criteria described in the USP paragraph <711>

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APPENDIX 1

PRELIMINARY STUDY

Table I : Mean Dissolution profile of 160 mg Fenofibrate Tablets (RG 2401/01) in 0.025 M SLS aqueous medium :

Paddle speed Time (minutes)	50 rpm Mean % dissolved (RSD)*	75 rpm Mean % dissolved (RSD)	90 rpm Mean % dissolved (RSD)	120 rpm Mean % dissolved (RSD)
10	53.8 (4.5)	64.5 (1.8)	65.5 (3.2)	68.1 (0.4)
15	69.5 (2.8)	77.6 (1.0)	79.7 (0.2)	80.9 (0.6)
20	78.0 (2.2)	84.8 (0.8)	86.9 (0.3)	87.4 (0.4)
30	85.9 (1.7)	91.0 (0.7)	92.8 (0.3)	93.1 (0.5)
40	90.2 (1.5)	94.1 (0.8)	95.8 (0.5)	95.7 (0.5)
50	92.9 (1.4)	96.1 (0.9)	97.6 (0.4)	97.3 (0.5)
60	94.6 (1.3)	97.4 (0.8)	98.6 (0.4)	98.4 (0.7)
120	99.4 (1.1)	100.4 (0.9)	101.0 (0.5)	100.5 (0.4)

Table II : Mean Dissolution profile of 160 mg Fenofibrate Tablets (RG 2401/01) in 0.05 M SLS aqueous medium :

Paddle speed Time	50 rpm mean % dissolved (RSD)	75 rpm Mean % dissolved (RSD)	90 rpm Mean % dissolved (RSD)	120 rpm Mean % dissolved (RSD)
10	71.0 (2.2)	78.9 (1.9)	81.5 (1.0)	85.6 (0.9)
15	85.0 (0.9)	91.5 (1.0)	93.0 (0.7)	95.5 (0.9)
20	91.6 (0.6)	97.2 (1.2)	97.5 (0.9)	98.3 (1.2)
30	96.9 (1.0)	99.8 (1..0)	100.2 (1.1)	101.2 (0.9)
40	99.2 (1.0)	101.7 (1.1)	101.4 (1.0)	101.3 (0.9)
50	100.8 (0.8)	Not performed	Not performed	102.5 (0.8)

Table III : Mean Dissolution profile of 160 mg Fenofibrate Tablets (RG 2401/01) in 0.1 M SLS aqueous medium :

Paddle speed Time	50 rpm Mean % dissolved (RSD)	75 rpm Mean % dissolved (RSD)	90 rpm Mean % dissolved (RSD)
10	80.9 (1.4)	88.3 (1.2)	88.9 (1.5)
15	91.7 (0.9)	98.7 (1.2)	99.7 (0.7)
20	96.4 (1.13)	101.8 (1.0)	102.0 (0.8)
30	100.1 (1.2)	Not performed	103.2 (0.8)

APPENDIX 2

DISCRIMINATORY ABILITY EVALUATION : HARDNESS STUDY

Table IV : Mean Dissolution profile of 160 mg Fenofibrate Tablets (RG 2401/01) in 0.025 M SLS aqueous medium at 75 rpm paddle speed.

Hardness Time (minutes)	147 N Mean % dissolved (RSD)*	206 N Mean % dissolved (RSD)
5	20.6 (6.0)	13.1 (6.6)
10	62.1 (3.2)	46.1 (3.7)
15	76.9 (0.7)	70.5 (1.2)
20	83.5 (0.9)	80.7 (1.0)
30	89.6 (0.5)	87.7 (1.1)
40	92.5 (0.8)	92.0 (0.5)
50	94.6 (0.6)	94.4 (0.4)
60	96.4 (0.6)	96.2 (0.8)
120	99.7 (0.8)	96.7 (0.5)

f1 associated value : 10.4

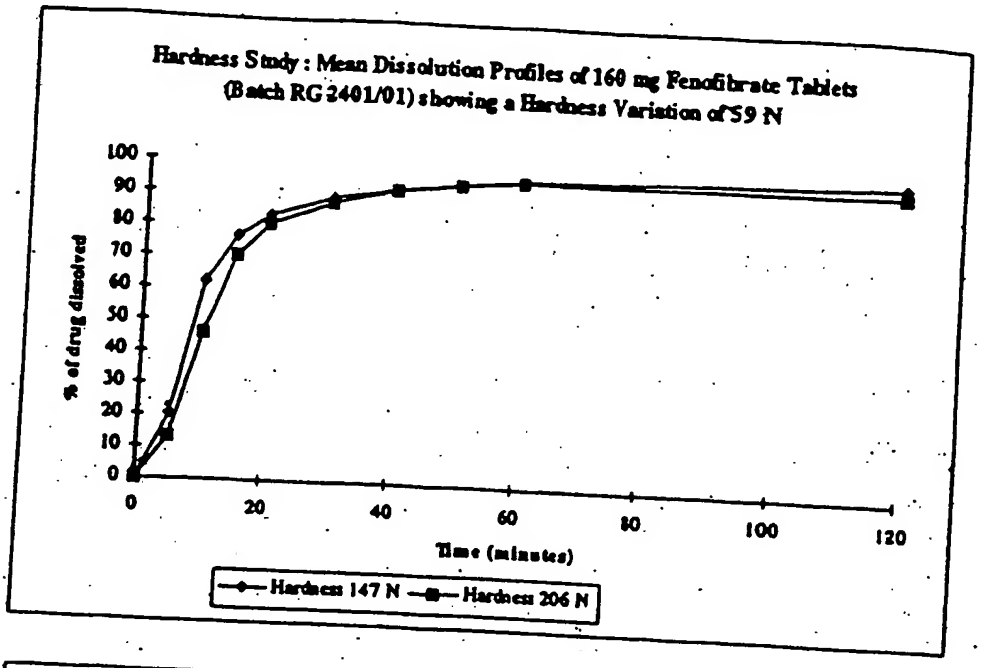
f2 associated value : 53.3

Table V : Mean Dissolution profile of 160 mg Fenofibrate Tablets (RG 2403/01) in 0.025 M SLS aqueous medium at 75 rpm paddle speed.

Hardness Time (minutes)	151 N Mean % dissolved (RSD)*	193 N Mean % dissolved (RSD)
5	19.9 (11.9)	16.8 (3.4)
10	60.7 (3.1)	53.5 (1.6)
15	76.7 (0.4)	73.6 (1.1)
20	83.9 (0.8)	82.5 (1.4)
30	90.1 (1.1)	88.9 (1.5)
40	93.6 (0.9)	92.2 (1.4)
50	95.1 (2.0)	94.1 (1.7)
60	96.7 (1.5)	96.1 (1.1)
120	99.9 (1.2)	98.7 (1.5)

f1 associated value : 4.8

f2 associated value : 70.0



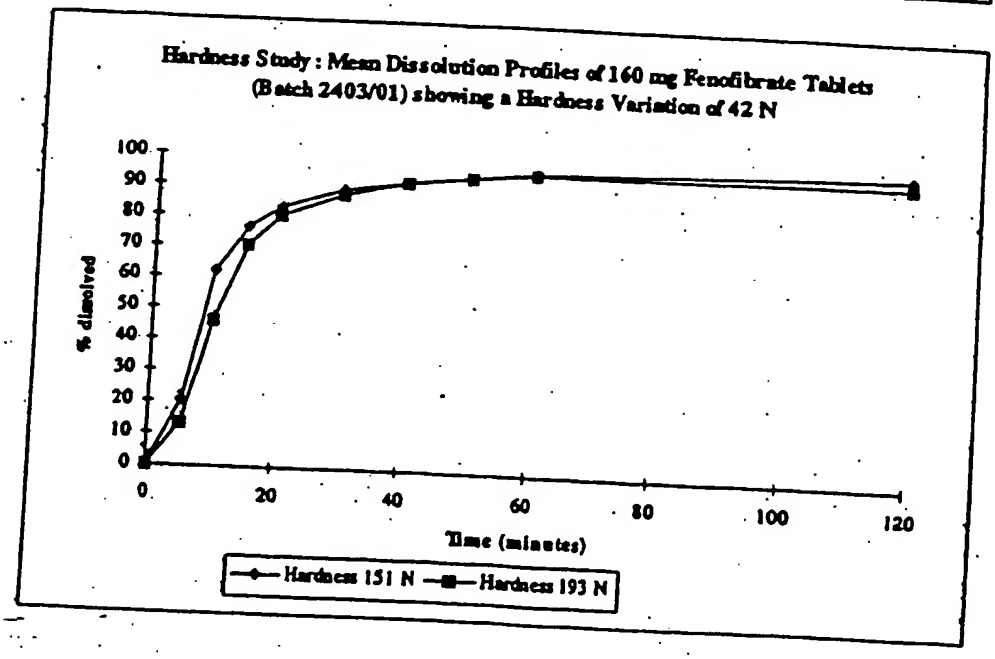


Table VI : Mean dissolution profile of Fenofibrate tablets tested at 0.05 M and 0.025 M SLS aqueous media at 75 rpm

Medium Strength batch number Time (minutes)	0.025 M 54 mg LF lot 2 Mean % dissolved	0.05 M 54 mg Abbott 47-800-AL Mean % dissolved	0.025 M 160 mg LF lot 7 Mean % dissolved	0.05 M 160mg Abbott 47-813-AL Mean % dissolved
10	74.2	80.1	48.9	63.9
20	93.4	93.6	85.4	96.8
30	97.7	97.5	94.7	100.6
40	98.8	98.8	98.0	101.4
50	100.1		99.4	
60	100.7		100.0	

Table VII : Mean dissolution profile of Fenofibrate capsules (TRICOR® 67 mg) tested at 0.05 M and 0.025 M SLS aqueous media at 75 rpm

Medium batch number Time (minutes)	0.025 M LF lot 032 Abbott 47-813-AL Mean % dissolved	0.05 M LF lot 032 Abbott 47-813-AL Mean % dissolved
5	8.1	
10	32.9	47.7
15	53.1	
20	64.4	75.9
25	71.3	
30	75.6	84.0
35	78.8	
40	81.2	88.2
50	84.3	
60	86.6	93.2
90	90.6	
120	93.42	

APPENDIX 3

COMPARATIVE ANALYSIS OF DISSOLUTION AND ABSORPTION DATA:

Table VIII : Mean Absorption profile (Loo Riegelman method) issued from bioavailability studies M98-961 and M 98-962

Product	Tablets	Capsules	Tablets	Capsules
Strength	54 mg	67 mg	160 mg	3 x 67 mg
Study	M98-961	M98-961	M98-962	M98-962
Time (hours)	Mean % Absorbed	Mean % absorbed	Mean % absorbed	Mean % absorbed
0	0.0	0.0	0.0	0.0
1	7.2	2.4	5.0	0.85
2	32.3	22.2	42.8	18.8
3	80.4	50.6	77.4	53.7
4	91.3	74.4	96.3	83.0
5	91.2	82.6	100.0	95.6
6	89.4	84.5	100.0	96.0
7	90.6	85.4	99.7	94.4
8	92.1	86.7	99.0	96.1
10	96.4	90.8	100.0	99.8
12	97.2	92.9	100.0	100.0
18	100.0	95.7	100.0	99.2
24	100.0	97.9	100.0	99.9

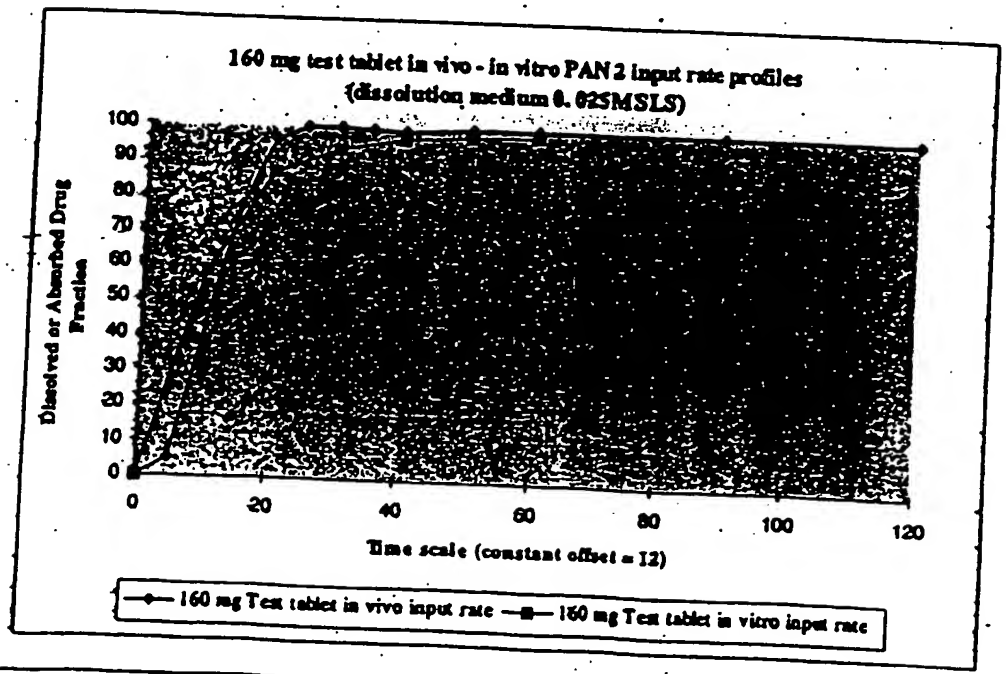
REPORT 137RAPDIS001 SUPPLEMENT N°1

Updating based on the Fenofibrate 160 mg tablets (LF lot number 7) dissolution raw data issued from the specific coating pan number 2 (lot fraction used to performed the bioavailability study M98-962).

Note : the initial report was based on dissolution data issued from pan 1 which was in consistent with the two other pans (numbers 3 and 4)

Table I addiff N°1 : Mean dissolution profile of Fenofibrate tablets 160 mg tested at 0.025 M SLS aqueous media at 75 rpm

Medium	0.025 M
Strength	160 mg
batch number	LF lot 7 (pan 2)
Time (minutes)	Mean % dissolved
10	48.9
20	85.4
30	94.7
40	98.0
50	99.4
60	100.0



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Dissolution Testing of LF 178 Ter Tablets

1. Selection of Dissolution Test Conditions

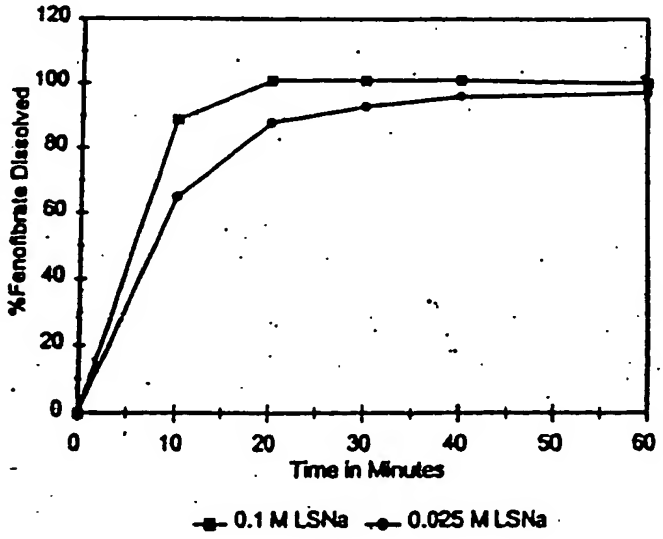
Due to the poor solubility of fenofibrate, less than 0.5 mg/L, the use of a surfactant such as sodium lauryl sulfate (LSNa) is necessary to be able to dissolve the fenofibrate content of the dosage form; 0.1 M aqueous sodium lauryl sulfate is presently used to test dissolution of Lipidil Micro® dosage. A preliminary study was carried out to determine the effect of the surfactant level on the rate and extent of LF 178 Ter tablet (160 mg fenofibrate) dissolution profiles.

The selection of the surfactant levels is based on solubility data of the drug substance in order to ensure either the sink condition (0.1 M) or a solubility close to the saturated solubility at the 160 mg dosage (0.025 M). The applied methodology consisted of:

- Paddle dissolution apparatus, complying with USP and EP
- 1000 mL of aqueous solutions of LSNa at 0.1 M or 0.025 M
- Paddle speed of 75 RPM
- Samples are collected every 10 minutes for 1 hour
- Fenofibrate assay by UV spectrophotometry

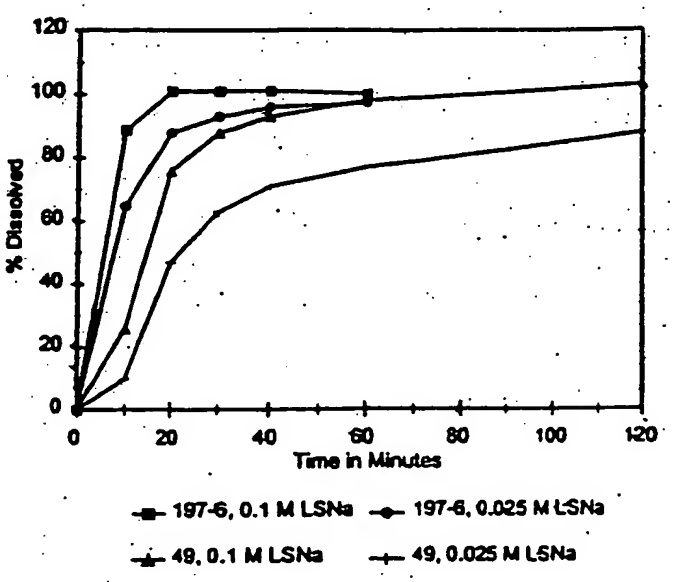
In both media, a complete dissolution of fenofibrate is achieved within 60 minutes (refer to the following figure).

Dissolution Profiles of LF 178 Ter Tablets (Batch 197-6) in Different Dissolution Media



In order to select the LSNa concentration, comparative dissolution of Lipidil Micro® (200 mg fenofibrate) and LF 178 Ter (160 mg fenofibrate) in both media was performed. Dissolution profiles are presented in the following figure. The difference in the dissolution profiles between the two dosage forms, which should be bioinequivalent if they had the same strength, is amplified when 0.025 M LSNa medium is used. For this reason, 0.025 M LSNa was selected for the dissolution of the LF 178 Ter tablets.

Dissolution Profiles of Lipidil Micro® (200 mg Fenofibrate Capsules, Batch 49) and LF 178 Ter Tablets (Batch 197-6)



From these studies the dissolution test conditions for LF 178 Ter tablets were set as:

- Paddle dissolution apparatus
- 1000 mL of 0.025 M aqueous LSNa solution
- Paddle speed of 75 RPM

2. Dissolution Specifications

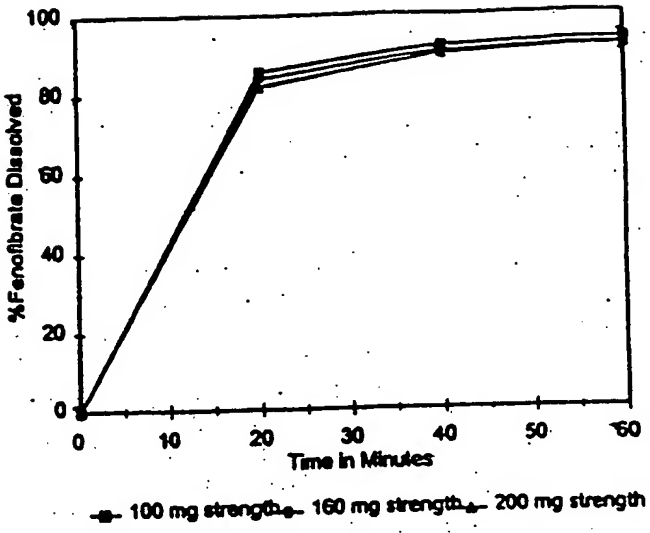
Pivotal bioequivalence Batch 197-6 of LF 178 Ter presents the following dissolution profile when tested under the above conditions.

Time (minutes)	0	10	20	30	40	60
Individual Results	0	65	89	96	97	99
	0	65	89	94	96	98
	0	66	89	95	96	98
	0	63	87	93	95	96
	0	63	88	93	95	98
	0	65	91	94	96	98
	0	69	89	94	96	97
	0	59	86	92	94	98
	0	62	87	93	95	97
	0	66	88	93	96	97
	0	69	88	94	96	98
	0	64	88	94	96	98
Average	0	64.7	88.3	93.8	95.7	97.7
SD	–	2.8	1.3	1.1	0.8	0.8
RSD	–	4.3	1.5	1.1	0.8	0.8

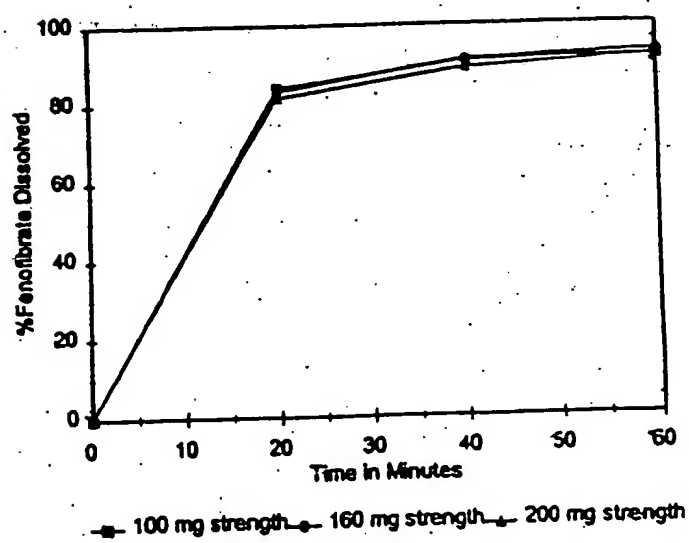
Time 40 minutes is selected to guarantee the rate and extent of the dissolution. At that time, the average dissolution observed on Batch 197-6 is 96%. A ±10% range is generally acceptable to specify the dissolution, which gives 86 to 106%; as +10% leads to a dissolved amount of fenofibrate above the label content, a Q approach, as defined in the USP, is selected. The corresponding Q value is 81%, which is rounded to 80%. Thus, the specification for the LF 178 Ter tablet (160 mg fenofibrate) dissolution test, throughout the shelf life, is $Q_{40\ minutes}$ = 80% where Q is defined in USP paragraph <711>.

Results of dissolution tests of the three different strengths of LF 178 Ter tablets, coated and non-coated, manufactured from the same bulk powder lots are presented in the following two figures.

Non-coated Tablets:



Coated Tablets:



The dissolution profiles of LF 178 Ter tablets containing 100 mg, 160 mg, or 200 mg fenofibrate are very similar. A small tendency to a slower dissolution (approximately 2% difference) is observed for the 200 mg tablets. This decrease in the dissolution rate for the 200 mg tablets is attributed to the fact that the fenofibrate concentration in the dissolution medium is nearing the saturation concentration. Nevertheless, the dissolution specification set for the 160 mg tablet, $Q_{30} = 80\%$, can be adopted for the LF 178 Ter tablets containing 100 mg or 200 mg fenofibrate.

SUMMARY

NAME OF STUDIED PRODUCT	LF 178 TER new tablet formulation of fenofibrate
TITLE OF THE STUDY	Single dose comparative bioequivalence study of two different formulations of fenofibrate (160 mg new tablet formulation versus LIPIDIL MICRO® 200 mg micronized fenofibrate) in 24 healthy male volunteers
INVESTIGATOR	Ewa Stasiak, M.D. LAB Pharmacological Research Intl. Inc.
STUDY LOCATION	LAB Pharmacological Research Intl. Inc. 1000 Ave. St. Charles Vaudreuil, Québec Canada J7V 8P6
STUDY AIM	To demonstrate the bioequivalence of two different formulations of fenofibrate (160 mg new tablet formulation versus LIPIDIL MICRO® 200 mg micronized fenofibrate) after a single oral dose given under fed conditions
CLINICAL PHASE	I
EXPERIMENTAL DESIGN	Randomized, blinded, 2-way crossover
NUMBER OF SUBJECTS TO BE INCLUDED	26
INCLUSION CRITERIA	Healthy male volunteers (18-35 years old)
FORMULATIONS, ROUTE OF ADMINISTRATION, DOSAGE	Modified micronized fenofibrate tablet Oral 160 mg Lot 197-6A
TREATMENT DURATION	2 single doses separated by a two-week wash-out period
EVALUATION CRITERIA	- Fenofibric acid plasma levels determined by HPLC (LOQ=30 ng/mL) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, 96 and 120h after each administration (n = 34; i.e. 360 mL blood volume per subject for pharmacokinetic purposes) - Pharmacokinetic parameters: AUC_t, AUC_∞, Cmax, tmax, $t_{1/2}$ and λ
STATISTICAL METHOD	- ANOVA on log transformed data (AUC_t, AUC_∞ and Cmax) - ANOVA on tmax and λ - 90% confidence interval about the mean AUC_t, AUC_∞ and Cmax
REFERENCE TREATMENT DOSAGE	Micronized fenofibrate (LIPIDIL MICRO®) Capsule Oral 200 mg Lot F49

OBJECTIVE

The objective of this study is to determine whether two different formulations of fenofibrate (160 mg new tablet formulation versus Lipidil Micro® 200 mg micronized fenofibrate capsules) from Fournier Pharma Inc. are bioequivalent under single dose, fed conditions.

STUDY DESIGN

Design:

Single-dose, randomized, blinded, 2-way crossover bioequivalence study in fed volunteers.

Treatments:

Treatment A: (test) One tablet containing 160 mg of a new formulation (LF 178 TER) of micronized fenofibrate.

Treatment B: (reference) One capsule containing 200 mg of micronized fenofibrate (LIPIDIL MICRO®)

Subjects:

A total of 27 healthy Caucasian male volunteers were enrolled, 24 of which completed the study. All subjects were non-smokers or smoked less than 10 cigarettes a day.

The methodology of a bioequivalence study requires that a homogeneous population be recruited to ensure a solid interpretation of the results. All previous fenofibrate bioequivalence studies were performed in men only. Maintaining this condition would facilitate comparisons among all the available studies.

Fasting/Meals:

Following a minimum 10-hour supervised overnight fast and 30 minutes prior to dosing, subjects were served a standard AHA breakfast. The breakfast consisted of cereal (40.0 g) with 100.0 mL 2% milk, one hard boiled egg, one slice of toast (15.0 g) with 10.0 g sunflower margarine, decaffeinated coffee (150.0 mL) and sugar (10.0 g). Meals were served at 4 hours after dosing, and at appropriate times thereafter; meal plans identical for each period. Water was permitted *ad lib.* until 2 hours before dosing and again at 4 hours after dosing.

Blood Samples:

Blood samples were collected immediately before breakfast (0 h) (2x7 mL), and at the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 18, 24, 48, 72, 96 and 120 hours (1x7 mL).

Blood Samples:

Blood samples were collected immediately before breakfast (0 h) (2x7 mL), and at the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 18, 24, 48, 72, 96 and 120 hours (1x7 mL).

Safety Assessments:

Subjects were given a complete physical examination including vital signs (supine and standing positions), body weight and urine test for drug of abuse after check-in in each period. Vital signs (supine and standing positions) and ECG were recorded prior to dosing in each period. At approximately 120 hours post dose in Period 2, subjects were given a complete physical examination including vital signs, ECG and clinical laboratory tests (excluding tests for HIV, drugs of abuse and blood alcohol). Blood pressure determination were performed 4 hours post dose.

Housing:

From at least 10 hours prior to dosing until after the 24-hour blood draw in each Period. Subjects return to LAB's screening facility for subsequent blood draws.

Washout Period:

Fourteen days between doses.

Analyte:

Plasma fenofibric acid (See Table 3 for a summary of the analytical method characteristics for this study).

ARCHIVES

All raw data generated in connection with this study, together with the original copy of the final report, will be retained in the Scientific Archives of LAB Pharmacological Research International Inc.

RESULTS AND DISCUSSION

The results of the bioavailability comparison are summarized in Tables 1 and 2 overleaf.

Observed Results

Limits of the 90% confidence intervals (two one-sided t-test method) for the observed data set (Table 1) are: 88% and 94% for AUC0-t, 88% and 95% for AUCinf and 85% and 94% for Cmax. The ratio of means for AUC0-t, AUCinf and Cmax are 91%, 91% and 89%, respectively. There were statistically significant differences for AUC0-t,

AUCinf and Cmax, mainly because the statistical power was such that small differences of 6%, 6% and 8% for AUC0-t, AUCinf and Cmax, respectively, could be detected as significant (Table 1). The ratio AUC0-t/AUCinf is approximately 98% for both formulations, demonstrating an adequate coverage of the AUC0-t by the sampling schedule.

Ln-Transformed Observed Results

Limits of the 90% confidence intervals (two one-sided t-test method) for the ln-transformed data set (Table 1) are: 88% and 94% for AUC0-t, 88% and 94% for AUCinf and 86% and 95% for Cmax. The ratios of means for AUC0-t, AUCinf and Cmax are 91%, 91% and 90%, respectively. There were statistically significant differences for AUC0-t, AUCinf and Cmax, mainly because the statistical power was such that small differences of 5%, 5% and 8% for AUC0-t, AUCinf and Cmax, respectively, could be detected as significant (Table 1).

Summary

The lower and upper confidence interval limits for AUC0-t, AUCinf and Cmax were within the 80% - 125% range.

Potency Adjusted Results

Potencies: Test: 98.7% Reference: 103.6%

Limits of the 90% confidence intervals (two one-sided t-test method) for the observed data set (Table 1) are: 88% and 95% for AUC0-t, 88% and 95% for AUCinf and 85% and 95% for Cmax. There were statistically significant differences for AUC0-t, AUCinf and Cmax, mainly because the statistical power was such that small differences of 6%, 6% and 8% for AUC0-t, AUCinf and Cmax, respectively, could be detected as significant (Table 1)

Potency Adjusted Ln-Transformed Results

Limits of the 90% confidence intervals (two one-sided t-test method) for the ln-transformed data set (Table 1) are: 92% and 98% for AUC0-t, 92% and 98% for AUCinf and 90% and 99% for Cmax. The ratios of means for AUC0-t, AUCinf and Cmax are 95%, 95% and 95%, respectively. There were statistically significant differences for AUC0-t, AUCinf and Cmax, mainly because the statistical power was such that small differences of 5%, 5% and 8% for AUC0-t, AUCinf and Cmax, respectively, could be detected as significant (Table 1).

Summary

The lower and upper confidence interval limits for AUC0-t, AUCinf and Cmax were within the 80% - 125% range.

TABLE 1
PROJECT GP527
SUMMARY OF STATISTICAL ANALYSIS - FENOFIBRATE
MEAN (C.V.%) BIOAVAILABILITY PARAMETERS
Observed Data
(n=24)

BIOAVAILABILITY PARAMETERS	A: LF 178 TER mean(C.V.%)	B: LIPIDIL MICRO mean(C.V.%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	90% CI Limits (%) Upper	Potency Adj. 90% CI Limits (%) Lower	Potency Adj. 90% CI Limits (%) Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. a=.05,B=.2
AUC0-t (mcg.hr/mL)	138.678 (26)	152.017 (24)	0.91	.0001 A<B	88	94	88	95	6	>99
AUCinf (mcg.hr/mL)	141.521 (27)	155.273 (25)	0.91	.0002 A<B	88	95	88	95	6	>99
AUC0-t/AUCinf	0.982 (1)	0.980 (1)	1.00	.4615 NS	100	101	105	106	1	>99
Cmax (mcg/mL)	7.983 (13)	8.923 (17)	0.89	.0014 A<B	85	94	85	95	8	>99
Tmax (hours)	3.875 (24)	4.417 (15)	0.88	.0101 A<B						
Kel (1/hours)	0.0361 (22)	0.0375 (24)	0.96	.1493 NS						
t½ (hours)	20.054 (21)	19.386 (21)	1.03	.1971 NS						

Observed Data (geometric means)

BIOAVAILABILITY PARAMETERS	A: LF 178 TER mean(C.V.%)	B: LIPIDIL MICRO mean(C.V.%)	Ratio of Means	ANOVA* p-value Treatment factor	90% CI Limits (%) Lower	90% CI Limits (%) Upper	Potency Adjusted Data A: Means	Potency Adjusted Data B: Means	Potency Adjusted Data Ratio of Means	Potency Adjusted Data 90% CI Limits (%) Lower	Potency Adjusted Data 90% CI Limits (%) Upper	Minimum(%) Detectable Difference (80%power)	POWER(%) to detect 20% difference. a=.05,B=.2
AUC0-t (mcg.hr/mL)	134.041 (27)	147.798 (24)	0.91	.00001 A<B	88	94	135.807	142.662	0.95	92	98	5	>99
AUCinf (mcg.hr/mL)	136.475 (28)	150.800 (25)	0.91	.00001 A<B	88	94	138.273	145.560	0.95	92	98	5	>99
Cmax (mcg/mL)	7.923 (13)	8.800 (17)	0.90	.0020 A<B	86	95	8.027	8.494	0.95	90	99	8	>99

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendices B1 & B3).

NS = (treatment effect) not significant at a=0.05 level. Differences based on Least Square Means test.

CI = Confidence Interval.

TABLE 2
Project GP527
MEAN PLASMA (C.V.%) FENOFIBRATE CONCENTRATIONS (mcg/mL)
AT EACH SAMPLING TIME POINT
Observed Data
(n = 24)

TIME (hours)	A: LF 178 TER mean(C.V.%)	B: LIPIDIL MICRO mean(C.V.%)	ANOVA* p-value Treatment factor	Statistically Significant Differences**
predose	0.000	0.000		
1 hour	1.459 (79)	0.465 (175)	0.0002	A>B
2 hours	5.331 (40)	3.349 (64)	0.0003	A>B
3 hours	6.980 (26)	6.773 (33)	0.6439	NS
4 hours	7.224 (20)	8.427 (20)	0.0010	A<B
5 hours	7.125 (15)	8.256 (14)	0.0001	A<B
6 hours	6.008 (17)	7.043 (13)	0.00001	A<B
7 hours	5.212 (17)	6.136 (15)	0.00001	A<B
8 hours	4.645 (19)	5.357 (16)	0.00001	A<B
10 hours	4.055 (21)	4.733 (17)	0.00001	A<B
12 hours	3.401 (22)	3.917 (19)	0.00001	A<B
18 hours	2.287 (32)	2.608 (26)	0.00001	A<B
24 hours	1.748 (29)	1.957 (29)	0.0002	A<B
48 hours	0.738 (48)*	0.852 (44)**	0.0215	A<B
72 hours	0.334 (60)*	0.361 (63)	0.2064	NS
96 hours	0.158 (78)	0.172 (72)**	0.6556	NS
120 hours	0.077 (93)	0.079 (93)*	0.9538	NS

*The ANOVA model has treatment, period, sequence and subject(sequence) as factors (see Appendix S2).

**NS = not significant at α=0.05 level. Differences based on Least Square Means test.

*n = 23.

**n = 22.